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Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England

John Marsden[1], Garry Stillwell[1], Hayley Jones[2], Alisha Cooper[3], Brian Eastwood[3], Michael Farrell[4], Tim Lowden[3], Nino Maddalena[3], Chris Metcalfe[2], Jenny Shaw[5] & Matthew Hickman[2]

Addictions Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK,[1] School of Social and Community Medicine, Faculty of Health Sciences, University of Bristol, Bristol, UK,[2] Alcohol, Drug and Tobacco Division, Health and Wellbeing Directorate, Public Health England, London, UK,[3] National Drug and Alcohol Research Centre, University of New South Wales, New South Wales, Australia[4] and Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK[5]

ABSTRACT

Background and Aims People with opioid use disorder (OUD) in prison face an acute risk of death after release. We estimated whether prison-based opioid substitution treatment (OST) reduces this risk. **Design** Prospective observational cohort study using prison health care, national community drug misuse treatment and deaths registers. **Setting** Recruitment at 39 adult prisons in England (32 male; seven female) accounting for 95% of OST treatment in England during study planning. **Participants** Adult prisoners diagnosed with OUD (recruited: September 2010–August 2013; first release: September 2010; last release: October 2014; follow-up to February 2016; n = 15 141 in the risk set). **Intervention and Comparator** At release, participants were classified as OST exposed (n = 8645) or OST unexposed (n = 6496). The OST unexposed group did not receive OST, or had been withdrawn, or had a low dose. **Measurements** Primary outcome: all-cause mortality (ACM) in the first 4 weeks. Secondary outcomes: drug-related poisoning (DRP) deaths in the first 4 weeks; ACM and DRP mortality after 4 weeks to 1 year; admission to community drug misuse treatment in the first 4 weeks. Unadjusted and adjusted Cox regression models (covariates: sex, age, drug injecting, problem alcohol use, use of benzodiazepines, cocaine, prison transfer and admission to community treatment), tested difference in mortality rates and community treatment uptake. **Findings** During the first 4 weeks after prison release there were 24 ACM deaths: six in the OST exposed group and 18 in the OST unexposed group [mortality rate 0.93 per 100 person-years (py) versus 3.67 per 100 py; hazard ratio (HR) = 0.25; 95% confidence interval (CI) = 0.10–0.64]. There were 18 DRP deaths: OST exposed group mortality rate 0.47 per 100 py versus 3.06 per 100 py in the OST unexposed group (HR = 0.15; 95% CI = 0.04–0.53). There was no group difference in mortality risk after the first month. The OST exposed group was more likely to enter drug misuse treatment in the first month post-release (odds ratio 2.47, 95% CI = 2.31–2.65). The OST mortality protective effect on ACM and DRP mortality risk was not attenuated by demographic, overdose risk factors, prison transfer or community treatment (fully adjusted HR = 0.25; 95% CI = 0.09–0.64 and HR = 0.15; 95% CI = 0.04–0.52, respectively). **Conclusions** In an English national study, prison-based opioid substitution therapy was associated with a 75% reduction in all-cause mortality and an 85% reduction in fatal drug-related poisoning in the first month after release.

Keywords All-cause mortality, drug-related poisoning mortality, heroin, opioid-use disorder, opioid substitution treatment, prison.

Correspondence to: John Marsden, Addictions Department, Box 48, Institute of Psychiatry, Psychology and Neuroscience, King's College London, DeCrespigny Park, Denmark Hill, London SE5 8AF, UK. E-mail: john.marsden@kcl.ac.uk
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INTRODUCTION

Non-medical opioid use contributes significantly to the global burden of disease [1]. Illicit heroin is associated with a high risk of death (particularly among people who inject drugs [2]), and this increases with age and in men [3]. The leading cause of death in this population is accidental drug poisoning (overdose) associated with acute respiratory

depression, hypoventilation and hypoxia [4]. In many countries opioid overdose is a major public health problem. The United States saw a fourfold increase in opioid poisoning deaths between 1999 and 2009 [5]. In England and Wales, the highest ever mortality rate from drug poisonings was recorded in 2015: 43.8 cases per million population [6].

There is a very high prevalence of substance misuse in the prison population (globally: 10–48% for men and 30–60% for women [7]). Of concern is that prisoners with OUD face an acute risk of death on their release to the community. This is particularly high during the first month [8,9], and there is evidence that an elevated risk is seen across the first year [10].

There are likely to be several causes. The most likely physiological mechanism is that the reduction, or complete reversal, of opioid tolerance during incarceration means that ex-prisoners are acutely vulnerable to fatal overdose if a pre-incarceration dose is consumed at liberty. Research has identified behavioural factors that also contribute: injecting an opioid increases drug bioavailability and respiratory effects acutely, and concurrent alcohol and benzodiazepine use can exacerbate suppression of the respiratory drive [11,12];. Although concurrent cocaine use (common among illicit heroin users in the United Kingdom, United States and several other countries) can briefly antagonize respiratory suppression, this stimulant can induce life-threatening cardiovascular arrhythmias. Taken together, fatal drug-related poisoning (DRP) in this population can have a relatively straightforward or a more complex cause [13].

Oral methadone and buprenorphine are the first-line opioid agonist therapies for opioid use disorder (OUD; DSM-5 [14] or the conceptually identical 'opioid dependence' diagnosis in ICD-10 [15]). These opioid substitution treatment (OST) medications are associated with cessation or lower drug use and injecting [16], a lower risk of acquiring blood-borne viral infections [17] and reduced mortality in the community setting [18,19]. Most national health-care systems offer OST for OUD. In England, illicit heroin is the main drug used by the OUD population, and OST (with adjunctive psychosocial interventions) is accessible in all local treatment systems [20].

Between 2006 and 2010, an integrated drug treatment system (IDTS) was introduced to provide OST in English prisons and to guide referral of prisoners to community drug misuse treatment services after their release [21]. OST in the IDTS involves oral methadone or buprenorphine for maintenance and (as indicated) withdrawal. Treatment is offered on a voluntarily basis according to a clinical assessment and the patient's preference. OST is provided as continued maintenance from the community (or another prison), or as a new episode beginning at entry, or during incarceration. Prisoners receive an initial clinical screening by a member of the health-care team and OUD diagnosis is confirmed by a doctor. The patient is then inducted onto OST as indicated.

With prison-based drug misuse treatment interventions intended to mirror and link to the provision of treatment in the community, case descriptive information on all treatment episodes is now captured by the English National Drug Treatment Monitoring System (NDTMS). NDTMS includes almost all publicly funded service providers and provides outcome and performance monitoring for each local treatment system [22].

Does prison-based OST exposure reduce post-release mortality? In 2012, a systematic review of six experimental and 15 observational studies concluded that there was limited evidence [23]. This was because studies either lacked a means of identifying prisoners with OUD and who had had OST or were unable to record overdose risk factors and subsequent treatment to isolate a treatment effect. English prison health-care records and the NDTMS capture all this information enabling a robust observational, cohort design with statistical control of confounders. An experimental design (i.e. patients assigned to OST maintenance or withdrawal before prison release) was rejected because medication is received voluntarily in the IDTS, and we considered it unethical to enforce withdrawal.

Accordingly, in this large-scale national study our aims were:

1 to estimate whether prison-based OST exposure at release reduces post-release mortality;
2 to estimate and compare the likelihood of admission to community drug-misuse treatment by OST exposure; and
3 to estimate whether a protective effect of prison-based OST at release is confounded by relevant covariates and admission to community treatment.

METHODS

Design, prison sample, target population and exposure

This was an English national prospective observational cohort study of prison-based OST exposure, reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [24].

In 2009, routine OST prescribing data compiled by the National Treatment Agency for Substance Misuse was used to identify the population of prisons providing OST. Forty-five prisons provided OST during that year. However, two had very small case-loads (i.e. < 4 new episodes of treatment initiated per quarter), so we decided to exclude these. Forty-three prisons were

approached to take part in the study (35 male prisons and eight female prisons).

The target population was adult prisoners (≥ 18 years) with a diagnosis of OUD recorded on an electronic database at the prison. Allocation of the patient to methadone or buprenorphine is guided by clinical assessment and patient preference in the IDTS. Patient preference is usually informed by personal experience or beliefs about these medications; clinical history of response and drug–drug interaction issues with other medication may also point to one medication over the other.

During planning, we were aware that some patients were released from prison with a low-dose prescription for methadone or buprenorphine. Efficacy trials of OST have included participants receiving 20–120 mg/day (methadone) and 2–16 mg/day (buprenorphine) [25]. Accordingly, we set > 20 mg for methadone and > 2 mg for buprenorphine as the dose threshold for classifying OST exposure for all prisoners at release.

Prisoners who met the threshold (i.e. their last dose administered on the morning of release was > 20 mg methadone or > 2 mg buprenorphine) were classified as OST exposed. Prisoners with OUD who had not received OST in prison, or had completed a medication withdrawal regimen while in prison, or had been prescribed less than the dose threshold on the day of release, were classified as OST unexposed.

Given the fluctuating nature of the English prison population—with people entering, some transferred to another prison, leaving, and some re-incarcerated—we expected a proportion of the study cohort to enter the risk set more than once during recruitment (see Statistical analysis).

Outcome measures

We selected all-cause mortality (ACM) in the first 4 weeks following release (i.e. days 1–28), expressed as risk per 100 person years (py), as the appropriate primary outcome measure. The null hypothesis was that there would be no difference in the ACM risk between the OST exposed and OST unexposed groups.

Secondary outcome measures (also tested as null hypotheses) were as follows: (1) DRP mortality in the first 4 weeks following release (expressed as risk per 100 py) and (2) ACM and DRP mortality after 4 weeks–1 year (expressed as risk per 100 PY); and admission to community drug misuse treatment in the first 4 weeks following release. DRP deaths were classified by the Office for National Statistics' definition [26] using the following codes from ICD-10 and referencing the coroner's inquest report and death certificate:

- Mental and behavioural disorders due to drug use (ICD-10 codes: F11-F16, F18, F19);
- Accidental poisoning by drugs, medicaments and biological substances (X40-X44);
- Intentional self-poisoning by drugs, medicaments and biological substances (X60-X64);
- Assault by drugs, medicaments and biological substances (X85); and
- Poisoning by drugs, medicaments and biological substances, undetermined intent (Y10-Y14).

Sample size calculation

For the first 4 weeks, pooled risk estimates from two previous studies [8,27] suggested that there would be 3.4 deaths per 100 py compared to 0.7 per 100 py for adults with OUD in the community. We estimated that a sample of 20 000 (50% OST exposed) would give at least 90% power to detect a fivefold or greater reduction in the mortality rate associated with prison-based OST exposure.

Procedure

We secured National Health Service research ethical approval for a recruitment procedure in which prison health-care staff would identify and approach eligible prisoners and obtain their informed, signed consent.[1] Of the 43 prisons approached to participate in recruitment, four prisons (three male and one female) were unable to take part because of the anticipated administrative burden or health-care staff shortages.

We provided on-site training on the study protocol for the remaining 39 prisons (32 for men and seven for women). As a check on representativeness, we noted that these institutions accounted for 95% of OST treatment in England during the study planning phase. As part of efforts to ensure that people would not feel obligated to take part, we stressed to the health-care teams that prisoner participation was voluntary.

Cohort recruitment started in September 2010. By April 2011 it was evident that we were not achieving the required level of recruitment. With the study steering committee's agreement, we proposed to retain data to this point and then adopt a non-explicit consent procedure. This would involve display of posters at multiple points throughout each prison presenting study information and stating that eligible prisoners receiving OST would be included unless they requested to opt out. We provided in-prison training with health-care staff on this procedure so that they would alert each prisoner who met the inclusion criteria to the poster and answer questions, and also discuss the study with those needing help with written English.

[1]Essex NHS Research Ethics Committee (reference: 10/H0302/7; February 2010).

This change was approved by the National Information Governance Board in August 2011,[2] by the original ethics committee in November 2011 and by all local research governance offices in June 2012. Recruitment recommenced under these arrangements in June 2012 and was completed in August 2013.

Data sources

Information was collected from five centralized and local data sources, as follows:

- Prison National Offender Management Information Service (P-NOMIS): prison where recruited; name, sex, date of birth (age grouped for analysis as follows: < 30; 30–34; 35–39; ≥ 40 years);
- Prison IDTS health-care provider: OST medication; dose at release; date of last dose if withdrawal regimen provided;
- Justice Statistics Analytical Services (JSAS database): name of releasing prison and date;
- Office for National Statistics, national deaths register, accessed from the Health and Social Care Information Centre (HSCIC): date of death and specified ICD-10 codes);[3]
- English National Drug Treatment Monitoring System (NDTMS): route of drug administration (injecting/other route); prisoner self-report of problem alcohol use; non-medical benzodiazepine use; cocaine use (all for past month before incarceration); date of admission to community drug misuse treatment (all types of structured interventions including OST) within 4 weeks following release.[4]

Participant recruitment

During the recruitment period (September 2010–August 2013) each person was assigned a study identification number. As noted above, participants could be recruited multiple times (i.e. on each occasion of incarceration during the recruitment period). The risk set was identified in three stages, as follows.

Stage 1

Prison health-care services identified an initial sample of 22 623 prisoners. Of these, 567 were removed because they were administrative duplicates on P-NOMIS (Prison National Offender Management Information System), and 56 people opted out and withdrew their consent.

Among the remaining 22 000 prisoners, 9093 (41.3%) were convicted and sentenced, 7956 (36.2%) were on remand awaiting trial and 1612 (7.3%) were incarcerated for another reason (e.g. failure to meet conditions of probation). Sentence type information was not recorded for the remaining 3339 prisoners (15.2%). In total, we recruited 3769 participants (17.1%) by individual consent and 18 231 by the 'opt-out' procedure (82.9%).

Stage 2

From the JSAS database, 1368 of 22 000 people recruited were removed because they did not leave prison, and a further 2186 were removed because a prison release date could not be verified. At completion of this stage, 18 446 prisoners were successfully matched to a release date.

The number of prisoners recruited from the 39 recruiting prisons ranged from 41 to 1704, and the number of prisoners released from prisons ranged from 40 to 1366. An additional 84 prisons (79 male and five female prisons) released 3184 prisoners (17.2%) due to transfer across the system.

Stage 3

Of the 18 446 releases identified in stage 2, HSCIC could flag 96% for monitoring on the deaths register (a loss of 770 people). After gathering all available OST information from IDTS health-care records, we removed a further 2527 releases because there was no medication information recorded, or because the health-care provider was unable to undertake a manual search. Eight people were also removed because they had died in prison.

At completion of this procedure, the risk set comprised 15 141 releases (relating to 12 260 people). The first release was in September 2010 and the last was in October 2014. We were notified of deaths by the HSISC until February 2016.

Statistical analysis

All analyses were conducted in Stata version 14. The data contained one or more exposure and risk periods for each person. Risk periods were censored at the earliest date of re-entry into the study or 1 year after release date. Kaplan–Meier 1-year survival curves were plotted.

We fitted a Cox proportional hazards model, stratified by post-release period, to estimate hazard ratios (HR), with associated 95% confidence intervals (CI) for the ACM and DRP deaths during days 1–28, months 2–4 (days 29–121) and months 5–12 (days 122–365). The assumption of proportional hazards within each of these periods was evaluated by plotting Nelson–Aalen

[2]Reference: ECC 5–04[d]/2011.

[3]There are extensive checks on accuracy for HSCIC, but it is possible in all studies of this kind in England that in a small number of deaths, the person died abroad and there was a failure of registration.

[4]The search for community treatment in NDTMS used a probabilistic case matching protocol [28].

cumulative hazard estimates and testing for a linear relationship between scaled Schoenfeld residuals and logged time within each period [29]. Random-effects (shared frailty) terms were included to adjust for potential clustering by prison of release.

In addition to the unadjusted (crude) HRs, the following covariates (overdose risk factors) were included in a multivariable Cox regression for the 4-week mortality outcomes: sex; age group; drug injecting; problem alcohol use; non-medical benzodiazepine use; and cocaine use. We adjusted for the potential confounding factor of prison transfer (i.e. people released from a different prison to the one at entry), hypothesizing that transfer could be associated with a reduced likelihood of OST exposure at release.

Admission to community drug misuse treatment during the first 4 weeks was also incorporated as a time-varying covariate to test whether any effect of OST exposure at release could be accounted for by subsequent treatment. If no NDTMS record for community treatment could be found, the released prisoner was assumed not to have been admitted. The likelihood ratio test (LRT) was used to test for evidence of mediation for community treatment and OST exposure on mortality risk. To assess further whether community treatment might be a mediator in any association between OST exposure and 4-week mortality, we fitted an additional Cox proportional hazards model with time to community treatment as the outcome variable (and OST at prison release as the exposure). For this analysis, risk periods were censored at the earliest point during the first 4-weeks post-release, at re-entry into the study population, or death.

So that all releases could contribute to the analysis, we multiply imputed missing covariate values using chained equations, assuming the missing values to be missing-at-random. Model estimates were based on 50 sets of imputed values and included the outcome measure, admission to community treatment, the estimated cumulative hazard for mortality and community treatment and all other covariates [30,31].

There were three sensitivity checks: first, the analysis was repeated using only those releases with complete covariate information (a 'complete case' analysis). Secondly, we checked that the multiple prison releases of some people did not lead to spuriously precise results. Here, the 'conditional gap time method' was used to stratify the baseline hazard by order of appearance in the study [32]. Finally, we compared the mortality risk from the time of entry to the study to 1 year, for releases that were linked to the deaths register but had missing information on prison release or OST exposure.

RESULTS

Among the 12 260 people in the risk set, 82.1% entered the study once. The remainder entered the study between two and seven times by re-incarceration (n = 2194).[5] The median time from recruitment to release was 60 days [interquartile range (IQR) = 28–156 days].

Intervention exposure and participant characteristics

We classified 8645 releases (57.1%) as OST exposed. Of these, 7614 (88.1%) received methadone [median daily dose on the day of release was 40 mg (IQR = 30–50 mg)] and 1031 (11.9%) received buprenorphine [median dose 8 mg (IQR = 8–12 mg)]. A minority of the OST exposure group was released from a different prison to the prison of recruitment (n = 942; 10.9%).

The remaining 6496 releases (42.9%) were classified as OST unexposed. These included 2369 people (36.5%) prescribed lower daily dose medication; 2110 (32.5%) who had been withdrawn from OST in prison; and 2017 (31.0%) diagnosed with current OUD but with no record of OST.

Table 1 shows the characteristics of the study participants in the intervention and comparator groups. The proportion of women was greater in the OST exposed group (24.1 versus 19.3%), due to proportionately more women's prisons agreeing to participate in the study and relatively higher individual participation rates within these institutions. The OST exposed group had a higher proportion of people who injected drugs, used non-medical benzodiazepines and cocaine and a lower proportion of problem drinkers.

Post-prison release mortality

Within the first year of release there were 160 deaths, 102 (63.8%) of which were DRP (mortality rate: 1.22 and 0.78 per 100 py, respectively). The other 58 deaths were recorded as: suicide and other injury (n = 22); liver disease due to viral hepatitis or alcohol (n = 13); drug injection-related infection (n = 5); respiratory disease (n = 8); cardiovascular disease (n = 7); and other non-communicable disease (n = 3).

Person follow-up time, mortality rates and number of deaths were as follows:

- 1–28 days (1133 py): ACM 2.12 per 100 py (24 deaths); DRP 1.58 per 100 py (18 deaths);

[5]More than half the re-incarcerated offenders were sentenced, with the remainder remanded or in prison for another reason (e.g. breaking probation conditions).

Table 1 Demographic and characteristics of people in the risk set by intervention exposure status at prison release (n = 12 260).

	OST exposed (n = 6662)	*OST unexposed (n = 5598)*	*Odds ratio or mean difference (95% CI)*
Men, *n* (%)	5054 (75.9)	4515 (80.7)	0.75 (0.69 to 0.82)
Age, years (SD)	34.6 (7.1)	34.6 (8.0)	0.00 (−0.30 to 0.20)
Drug injecting, *n* (%)[a]	4167 (72.1)	2648 (56.3)	2.01 (1.85 to 2.18)
Missing data, *n* (%)	885 (13.3)	895 (16.0)	
Problem alcohol use, *n* (%)	1724 (28.7)	1763 (35.8)	0.72 (0.67 to 0.78)
Missing data, *n* (%)	660 (9.9)	675 (12.1)	
Non-medical benzodiazepine use, *n* (%)	1504 (25.0)	870 (17.6)	1.56 (1.42 to 1.71)
Missing data, *n* (%)	638 (9.6)	658 (11.8)	
Cocaine use, *n* (%)	2438 (40.5)	1741 (35.2)	1.25 (1.16 to 1.35)
Missing data, *n* (%)	638 (9.6)	658 (11.8)	

OST = opioid substitution treatment; CI = confidence interval; SD = standard deviation. [a]Injecting versus other route of drug administration (score: 1,0).

- 29–121 days (3521 py); ACM 1.14 per 100 py (40 deaths); DRP 0.68 per 100 py (24 deaths); and
- 122–365 days (8478 py); ACM 1.13 per 100 py (96 deaths); DRP 0.71 per 100 py (60 deaths).

The survival curve for the OST exposed and unexposed groups for ACM and DRP mortality is displayed in Figs 1 and 2, respectively.

Association between OST exposure and mortality

Among the 24 ACM cases within 4 weeks of prison release, six were members of the OST exposed group and 18 were members of the OST unexposed group [mortality rate 0.93 per 100 py versus 3.67 per 100 py; HR = 0.25, 95% confidence interval (CI) = 0.10–0.64)].

During the first 4 weeks, there were 18 DRP deaths. Three were members of the OST exposed group and 15 were members of the OST unexposed group (mortality rate 0.47 per 100 py versus 3.06 per 100 py; HR = 0.15; 95% CI = 0.04–0.53).

After the first 4 weeks, the mortality difference narrowed between the two groups (Supporting information, Fig. S1). There was no evidence of between-group difference in risk of ACM or DRP mortality during the second to fourth months (29–121 days) and from the fifth month to 1 year (122–365 days; Table 2). There was no evidence against the proportional hazards assumption within any of these three periods (minimum P-value 0.17) and no evidence of clustering of mortality by prison of release.

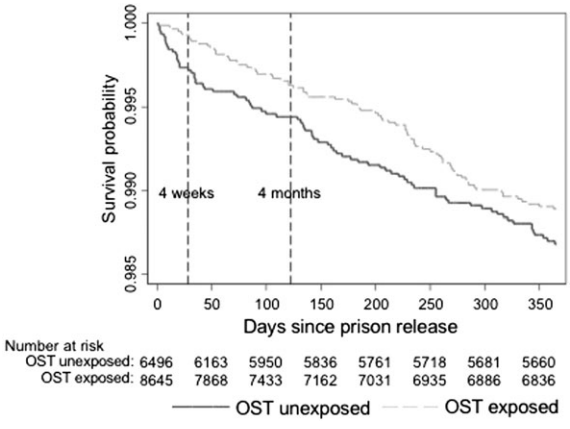

Figure 1 Survival curve during the year following release (all-cause mortality). OST = opioid substitution treatment

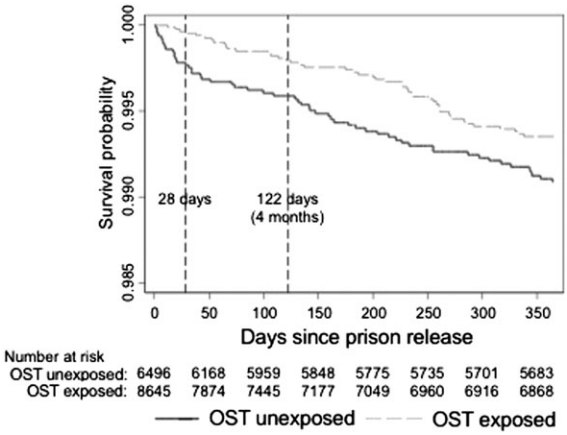

Figure 2 Survival curve during the year following release (drug-related poisoning mortality). OST = opioid substitution treatment

Multivariable model of OST exposure on mortality

Table 3 shows the unadjusted and adjusted analysis of OST exposure and mortality outcomes in the first 4 weeks. For ACM, the protective effect of OST exposure was not attenuated following adjustment for age and risk factors (adjusted HR = 0.24; 95% CI = 0.09–0.61) or by adjustment for community treatment (HR = 0.28; 95% CI = 0.11–0.71). The fully adjusted HR for all covariates, including prison transfer, was 0.26 (95% CI = 0.09–0.64). The protective effect of OST exposure on DRP mortality was similarly not attenuated (fully adjusted HR = 0.15; 95% CI = 0.04–0.52). There was also no evidence of mediation

Table 2 Person-years, mortality rates and hazard ratios for ACM and DRP mortality, by intervention exposure at prison release and follow-up period.

	OST exposed		*OST unexposed*		
Period	*py at risk (n deaths)*	*Rate per 100 py (95% CI)*	*py at risk (n deaths)*	*Rate per 100 py (95% CI)*	*HR (95% CI)*[a]
ACM					
1–28 days	643 (6)	0.93 (0.42–2.08)	490 (18)	3.67 (2.31–5.83)	0.25 (0.10–0.64)
29–121 days	1966 (23)	1.17 (0.78–1.76)	1555 (17)	1.09 (0.68–1.76)	1.07 (0.57–2.00)
122–365 days	4654 (52)	1.12 (0.85–1.47)	3824 (44)	1.15 (0.86–1.55)	0.97 (0.65–1.45)
DRP mortality					
1–28 days	643 (3)	0.47 (0.15–1.45)	490 (15)	3.06 (1.85–5.08)	0.15 (0.04–0.53)
29–121 days	1966 (13)	0.66 (0.38–1.14)	1555 (11)	0.71 (0.39–1.28)	0.93 (0.42–2.08)
122–365 days	4654 (31)	0.66 (0.47–0.94)	3824 (29)	0.76 (0.53–1.09)	0.88 (0.53–1.46)

ACM = all-cause mortality; DRP = drug-related poisoning; OST= opioid substitution treatment; py = person-years; CI = confidence interval; HR = unadjusted HR ratio. [a]There was no statistical evidence of non-proportional hazards within each period ($P > 0.05$).

Table 3 Covariate adjusted effect of OST exposure at prison release on ACM and DRP mortality in the first 4 weeks (n = 15 141).

Model	*ACM (primary outcome) HR (95% CI)*	*DRP mortality HR (95% CI)*
OST (unadjusted)[a]	0.25 (0.10–0.60)	0.15 (0.04–0.53)
OST + age group[b]	0.26 (0.10–0.65)	0.15 (0.04–0.53)
OST + injecting[c]	0.23 (0.09–0.59)[d]	0.14 (0.04–0.47)[d]
OST + problem alcohol use	0.26 (0.10–0.65)[d]	0.16 (0.05–0.54)[d]
OST + non-medical benzodiazepine use	0.25 (0.10–0.62)[d]	0.14 (0.04–0.50)[d]
OST + cocaine use	0.26 (0.10–0.66)[d]	0.16 (0.05–0.54)[d]
OST + demographic and clinical covariates	0.24 (0.09–0.61)[d]	0.14 (0.04–0.47)[d]
OST + prison transfer [e]	0.25 (0.10–0.63)	0.15 (0.04–0.51)
OST + community treatment[f]	0.28 (0.11–0.71)	0.17 (0.05–0.59)
OST + all covariates[g]	0.25 (0.09–0.64)[d]	0.15 (0.04–0.52)[d]

ACM = all-cause mortality; DRP = drug-related poisoning mortality; OST = opioid substitution treatment; HR = hazard ratio; CI = confidence interval. [a]OST exposed versus OST unexposed (scored: 1,0); [b]age group: < 30, 30 to 34, 35–39, ≥ 40 years (no missing observations); [c]injecting (current/life-time versus never; scored: 1,0); [d]multiply imputed analysis with all releases. These analyses did not include shared frailty terms (random effects) for prison of release; [e]prison of release different from recruitment prison; [f]admitted to community drug misuse treatment within 4 weeks (time-varying covariate); [g]i.e. all demographic, clinical, prison transfer and community treatment measures.

between community treatment and OST exposure on ACM (ratio of HR = 0.97; 95% CI = 0.12–7.97; LRT P-value 0.98) or DRP mortality (ratio of HR = 1.26; 95% CI = 0.07–21.29; LRT P-value 0.86).

Community drug misuse treatment

A total of 6140 releases (40.6%) were admitted to drug misuse treatment within the first 4 weeks. The OST exposed group was more likely to enter treatment than the unexposed group (odds ratio = 2.47, 95% CI = 2.31–2.65). Following adjustment for clustering by prison (P-value for clustering < 0.001), the HR for being admitted to treatment was 2.13 (95% CI = 2.01–2.25, with no evidence for non-proportional hazards, P-value 0.50; Fig. 3). There was no statistical association between

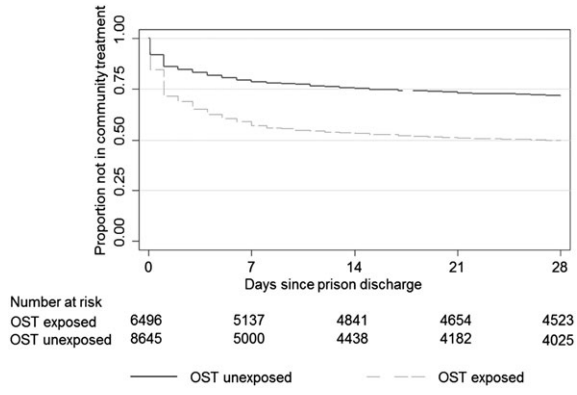

Figure 3 Time to admission to community drug misuse treatment in first 4 weeks after prison discharge by opioid substitution treatment (OST) prison exposure: Kaplan–Meier plot

community drug misuse treatment and the risk of ACM or DRP mortality (HR = 0.51; 95% CI = 0.19–1.39 and HR = 0.39; 95% CI = 0.11–1.36, respectively) and no evidence of non-proportional hazards (*P*-value 0.18 and 0.34, respectively).

Sensitivity analyses

With complete covariate information available on 86.9% of releases (missing observations for behavioural covariates: 10–16%), the 'complete case' analysis also showed a protective effect of OST exposure on mortality risk (Supporting information, Table S1).

In the check on multiple prison releases, we confirmed that multiple appearances of some study participants did not lead to spuriously precise estimates. With baseline hazard stratified by the participant's release number, the HR for the association between OST exposure and 4 week ACM was 0.27 (95% CI = 0.11–0.69).

There were 2082 releases linked to the deaths register with missing prison release information, and 2526 with missing OST exposure information. Excluding those not released, the mortality rate for the former group was 0.93 per 100 py compared to 0.92 per 100 py among those with no missing prison release information [incidence rate ratio (IRR) = 1.01; 95% CI = 0.43–2.05]. For the latter group the mortality rate was 1.57 per 100 py compared to 1.23 per 100 py among those with no missing OST exposure information (IRR = 1.27; 95% CI = 0.86–1.84).

DISCUSSION

In this national study, OST exposure with oral methadone or buprenorphine removed the fourfold excess risk of death in the first 4 weeks after release for prisoners with OUD. OST was associated with a 75% reduction in ACM and an 85% reduction in DRP mortality. The protective effect of OST was not observed after the first month. Those in the OST exposed group were more than twice as likely to be admitted to community-based drug misuse treatment in the first month.

The strengths of our study include: the large sample of prisoners with OUD; the use of administrative databases for recording OST exposure; outcome estimates subject to confounder control; and clinically important findings which apply to both the prison and community drug misuse treatment systems in England and elsewhere.

We also acknowledge several study limitations: first, we were unable to report on the numbers of eligible prisoners who were approached and declined to take part the overall proportion of prisoners enrolled in OST across the 39 prisons. However, we believe it was unlikely that the revised procedure in our prospective design introduced a selection bias in relation to OST exposure and future mortality risk, and we received very few requests to opt out.

Secondly, some cases had to be removed because of duplication of records and matching failures, and some prisons were unable to give information on OST medication. Missing OST exposure and prison release data will have reduced statistical power, and we did not have sufficient samples to compare outcomes for men and women. However, we do not believe case attrition was likely to have introduced bias to the estimate of mortality risk. The protective effect of OST was not sensitive to imputation of missing confounders, and we showed that there were no differences in mortality risk for prisoners with or without missing data on prison release or OST exposure.

Thirdly, OST exposure was not randomized. However, we show that differences in OST exposure for people who inject drugs, for those using other drugs and for those transferred between prisons did not alter the strength or direction of our findings. Our analyses tested and examined the impact of behavioural confounders and community treatment and found a mutually beneficial association with no evidence of any interaction or mediation. Furthermore, we believe a selection bias was highly unlikely, as the outcome had not occurred by the time exposure had been determined.

Results in context

The present findings align with a recent study of prison-based OST in New South Wales [33]. In this Australian study, the 4-week mortality rate after release comparing OST exposure and entry to community treatment versus no prison or community treatment was 0.64 and 3.67 per 100 py, respectively. This is a slightly stronger protective effect than we observed, but this may be due to the exposure in the Australian study being continuous OST from prison to community in the first month, and for a greater potential for immortal time bias in this retrospective cohort design [34].

A recent study conducted in Scotland reported an overall reduction in mortality risk after introduction of prison-based OST (from 3.8 to 2.2 per 1000 releases), but observed no protective effect for OST in the immediate period following release [35]. The researchers were unable to identify the OUD population in the prisons studied, nor adjust for risk factors, but they concluded that: 'in-prison OST does not reduce early deaths after release' (p. 1617). Our adjusted models provide strong evidence against this conclusion for England.

Meaning of the study and its implications

Physiological tolerance to opioids is the most likely mechanism of protective effect for people who leave prison

enrolled in OST with relapse vulnerability. If heroin is used there is a reduced likelihood of acute respiratory depression. OST will also prevent the onset of opioid withdrawal symptoms which may motivate illicit drug use.

How can the absence of protective effect after the first month following release be explained? We suspect that several factors are involved: some patients enrolled in community treatment will resume use of heroin, progressively returning to pre-prison levels; others will drop out of community treatment and relapse; and some people who are not enrolled in OST at release will present for community OST. Further studies are needed to explore these subpopulations and their trajectories and association with mortality outcome.

Given an increasing global prison population, effective initiatives are needed to improve prisoners' health and reduce the burden of infectious and chronic disease and other causes of premature mortality. Prison-based OST is scarce in the United States and there is little or no provision in many other countries. In this context, we frame our findings in the clinical management of OUD and prevention of overdose. First, the importance of continuity of OST from the community to the prison system is supported unequivocally by our findings. OST in prison enables prisoners to engage with recovery services and there are also important public health benefits. For example, a low incidence of hepatitis C virus has been reported in Scottish prisons with OST provision [35]. OST withdrawal regimens should not be overlooked, but we contend that withdrawing a patient in prison should be conducted with a careful appraisal of post-release support and with full discussion of the risks.

Secondly, for prevention of fatal opioid overdose, a specific *ex-post* strategy is the supply of the short-acting opioid antagonist naloxone to prisoners at release for acute administration in the community. This strategy has not been implemented in English prisons to date. Encouragingly, the first 2 years of the national naloxone programme in Scotland were associated with a 36% reduction in the proportion of opioid-related deaths that occurred in the first month after release [37].

Thirdly, for those with OUD who are abstinent from all opioids and have been informed appropriately and consented, there is also an opportunity to use the long-acting opioid antagonist, naltrexone, as an *ex-ante* relapse prevention therapy. A 50-mg tablet of naltrexone blocks the effects of opioids for approximately 24 hours; an extended-release, intramuscular injection is also available. This treatment has not been implemented systematically in English prisons and is not viable for everyone (e.g. contraindication in liver disease and for some with chronic non-malignant pain). However, the feasibility of extended-release naltrexone has been demonstrated recently in two open-label trials in the United States (one study using an injection before prison release; the other using monthly injections in the community) [38,39].

CONCLUSION

Opioid overdose is a major public health problem in many countries. People with OUD who reduce or stop using non-medical opioids while incarcerated face an acute risk of death on release if they use these drugs again. Our study shows that prison-based OST (with oral methadone or oral buprenorphine) is a highly effective means of reducing the risk of death among prisoners in the first 4 weeks after release. The clinical decision to withdraw prisoners from OST should be made with care and with further support.

Declaration of interests

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Transparency declaration

J.M. affirms that the manuscript is an honest, accurate and transparent account of the IDTS evaluation. H.J. and C.M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1 Plot of Nelson–Aalen estimates of cumulative hazard, comparing those opioid substitution treatment (OST) exposed and unexposed to 1 year months after prison release.

Table S1 Covariate adjusted effect of opioid substitution treatment (OST) exposure at prison release on all-cause mortality (ACM) and drug-related poisoning (DRP) mortality in the first 4 weeks: complete case analysis ($n = 13\,158$).